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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,332	04/07/1999	KAARE M. GAUTVIK	16777/309	6190

7590 02/27/2004

FOLEY AND LARDNER
3000 K STREET NW SUITE 500
WASHINGTON, DC 200075109

EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/287,332	GAUTVIK ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,39,41 and 57-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,39,41 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Amendment dated 12/31/03 has been entered into the record.

B. Claims 38, 39, 41 and 57-59 are pending and are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Specification

A. All objections to the specification have been withdrawn in view of Applicants' amendments.

3. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 38, 39, 41 and 57-59 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 2-3 of the Office Action dated 7/2/03. Applicants argue that the specification provides sufficient guidance for the use of signal sequences other than MFα1 with and without an STE13 mutation. Applicants provide examples of numerous leader sequences and argue that the artisan would be able to construct a microorganism using a leader sequence selected from these known sequences. These arguments have been considered, but are not deemed persuasive. It is clear from Applicants' specification that not only was PTH known, but that numerous leader sequences were also known at the time of Applicants' invention (page 3, lines 3-8 of the specification and pages 23-26). Therefore, it is not understood why it would not have been obvious to the artisan at the time of the present invention to have added a known leader sequence to PTH for expression in E. coli. Therefore, it appears that the process of expressing PTH from E. coli is not as easy as it would appear. Applicants have only disclosed that a small number of signal sequences appear to be functional in the present invention (page 14, lines 15-35). If PTH is easily degraded, it is not understood how such a wide variety of signal sequences, such as those disclosed on pages 23-26 of the specification, would increase the stability of this protein. Applicants are requested to explain this issue – i.e. if PTH and numerous signal sequences were known in the art at the time of the present invention, why it wasn't obvious at the time to produce stable PTH using these sequences and, if it wasn't obvious, how is it predictable to the artisan that the numerous signal sequences known in the art and taught in the specification would increase the stability of PTH. Again, Applicants disclose on page 4, lines 10-19 of the specification that the present invention uses a double start codon at

the 5'-end of the preproPTH which may aid in increasing yield. However, this is not required in the claims, nor does this appear to be required for intact secretion of PTH in E. coli or in yeast. The invention appears to be focusing only on the use of a cleavable leader sequence which will allow PTH to be secreted intact.

4. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claim 39 under 35 USC 112, second paragraph, has been withdrawn in view of Applicants' amendment to the claim to recite "consisting essentially of."

5. Obviousness-Type Double Patenting

A. The rejection of claims 38, 39, 41 and 57-59 appears to have been overcome by the submission of Terminal Disclaimers over U.S. Patent Nos. 5,420,242; 5,010,010 and 6,146,852. Applicants will be notified in a subsequent Action once these Disclaimers are processed and accepted.

B. Claims 38, 39, 41 and 57-59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over one or more claims of copending Application No. 08/340,664. Although the conflicting claims are not identical, they are not patentably distinct from each other since placing the protein in any of a number of solutions, such as buffer or water, would read on "cell-free medium." This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Request for Information

Applicant and the assignee of this application are required under 37 CFR §1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

The specification at page 7, line 10, teaches the use of an hPTH standard (1-84) to compare and assess the results of the purification process. The specification teaches that the purification product eluted in the same peak as this standard and co-migrated with the standard as one band on a gel. The specification implicitly asserts that these comparisons demonstrate the purity and completeness of the protein being claimed and that this standard would be known by the artisan to be maintained in a cell-free medium, such as buffer or water. Accordingly, applicants are requested to provide all pertinent information regarding the source of the protein used as a standard.

In responding to those requirements that require copies of documents, where the document is a bound text or a single article over 50 pages, the requirement may be met by providing copies of those pages that provide the particular subject matter indicated in the requirement, or where such subject matter is not indicated, the subject matter found in applicant's disclosure.

The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained will be accepted as a complete reply to the requirement for that item.

A complete reply to this Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the Office action.

7. Claim Rejections - 35 USC § 102

A. Claims 38, 39, 41 and 57-59 remain rejected under 35 USC 102 for the reasons already of record on page 4 of the Office Action dated 7/2/03. Applicants argue that the examiner has not provided any scientific evidence that any PTH leaked into the medium from the cells of Breyel et al. However, since the Office does not have the facilities for examining and comparing applicants' medium with the medium of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not secrete into the medium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Applicants also argue that the cell-free medium of the present invention is distinct from that of the extract of Breyel et al. However, regardless of the definition of "cell-free extract," or what the extract of Breyel teach, the fact still remains that PTH, a protein normally secreted from cells, would be expected to be secreted from intact cells in culture.

B. Claims 38, 39, 41 and 57-59 are rejected under 35 U.S.C. 102 (a), (b) and/or (f) as being anticipated by applicants admission of the prior art.

The specification at page 7 teaches the use of an hPTH standard (1-84) to compare and assess the results of the purification process. The specification teaches that the purification product eluted in the same peak as this standard and comigrated with the standard as one band on a gel. The specification implicitly asserts that these comparisons demonstrate the purity and completeness of the protein being claimed. In order for the "standard" to have been useful for such comparison, it itself must have met the limitations of the pending claims. The artisan would immediately envision the purified PTH in a buffer, or water, especially in view of the fact that this protein would need to be solublized to be run on a gel. Therefore, this protein would be in a cell-free medium.

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38, 39, 41 and 57-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Breyel et al. (3rd Eur. Cong. Biotech., cited by appellants) or Mayer et al. (EP 0 139 076, cited by appellants), any reference of the three in view of Kaisha et al. (GB 2 092 596, cited by appellants), and Brewer et al., U.S. Patent Number 3,886,132.

Breyel et al. teach expression of mature hPTH in *E. coli*, see Summary, page 363. The protein was expressed and bacterial cell extracts assayed for activity, see page 366 for example. Breyel differs from the instant claims only in that the protein was not purified from the bacterial cell extracts.

Mayer et al. teach recombinant production of hPTH in *E. coli*, see page 9, first full paragraph for example, page 12 of the enclosed English-language translation. The protein was purified from the cells and shown to be biologically active. Mayer et al. do not teach purification to the degree recited in the rejected claims.

Kaisha et al. teach a process for the production of hPTH. Although their patent is not drawn to recombinant production using bacterial or yeast cells, they disclose at page 2, first column, beginning at line 55 that:

> "The hPTH thus obtained can be collected easily by purification and separation techniques using conventional procedures such as salting-out, dialysis, filtration, centrifugation, concentration and lyophilisation. If a more highly purified hPTH preparation is desirable, a preparation of the highest purity can be obtained by the above-mentioned techniques in combination with other conventional procedures such as adsorption and desorption with ion exchange, gel filtration, affinity chromatography, isoelectric point fractionation and electrophoresis."

Thus, Kaisha et al. teach the desirability of making large quantities of hPTH, and that the person of ordinary skill in the art, given a preparation containing hPTH, would be able to devise a protocol for purifying such with a reasonable expectation of success and without undue experimentation.

Brewer et al. specifically teach a protocol for purifying hPTH from its natural source, parathyroid tissue, see column 2, lines 3-13. As stated in the rejection under 35 U.S.C. §102(b) and affirmed by the BPAI, the hPTH so purified meets the purity limitations of the claims.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to express hPTH as taught by Breyel et al. or Mayer et al., and then to purify the hPTH so produced as suggested by Kaisha et al., such as using the protocol of Brewer et al. to obtain highly purified hPTH. The ordinary artisan would have been motivated to do so in view of the art recognized desirability of obtaining hPTH in pure form, as evidenced by all four cited references. As both Breyel and Mayer obtained at least partially purified preparations, the person of ordinary skill in the art would have recognized that such preparations could be further purified using the protocol of Brewer et al. The teachings of Brewer et al. indicate that the ordinary artisan would have had at least a reasonable expectation of success at purifying hPTH once produced as taught and/or suggested by Breyel or Mayer. Accordingly, the claimed invention, taken as a whole, is *prima facie* obvious over the cited prior art. The artisan would immediately envision the purified PTH in a buffer, or water, especially in view of the fact that this protein would need to be solublized to be run on a gel. Therefore, this protein would be in a cell-free medium.

9. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 19, 2004

ROBERT LANDSMAN
PATENT EXAMINER